CONGENITAL ANOMALIES AND ENVIRONMENTAL EXPOSURES

ANOMALIE CONGENITE
ED ESPOSIZIONI AMBIENTALI

INDUSTRIES
INDUSTRIE

A retrospective cohort study performed in Colorado between 1996 and 2009 investigated the maternal exposure to emissions from natural gas wells (within a 10-mile radius from residence), comparing the exposed population with the unexposed population based on both the number of wells within the 10-miles radius and the proximity to the mother's residence. Results revealed a monotonic increase in the prevalence of congenital heart defects (CHDs) in babies, correlating with increasing density and proximity of shale gas to the mother's residence (table 2). Infants born to exposed mothers had a 30% higher risk of CHDs compared to the offspring of unexposed mothers in a similar area without wells. Infants born to exposed mothers showed increased risks compared with the unexposed group; namely, a 400% increase of the tricuspid valve defects, 60% increase of pulmonary valve stenosis (PVS), and 50% increase of ventricular septal defects (VSDs) were observed. A slight increase of neural tube defects (NTDs) among babies born to the most exposed mothers (over 125 wells per mile) was found.[29]

In Texas, association between maternal residential proximity to emissions of chlorinated solvents and selected CAs in their offspring (CHDs, NTDs, cleft lip/palate, limb reductions) was assessed in a case-control study performed on births occurring between 1996 and 2008. The study investigated effects linked to the maternal residential distance from industrial areas or linked to the amount of solvents released from each source on a yearly basis.[30] Results detected a slight increase in risk of cardiac septal defects (CSDs) in babies born to mothers exposed to solvents (any type) compared to the unexposed group. An increase was found for NTDs, especially for spina bifida among babies born to mothers exposed to several chlorinated solvents (e.g., carbon tetrachloride, chloroethane, chloroform). Weak associations were also observed between propylene dichloride and cleft palate and between perchloroethylene and limb reduction defects. Among mothers aged 35 years or older, the associations between maternal residential exposures to chlorinated solvents emissions and development of CAs, especially cleft lip and palate and obstructive cardiac defects, were higher, suggesting that mother's age may increase susceptibility of the developing foetus to the adverse effects of chemical pollutants.[30]

The results from an ecological study on babies born to mothers resident close to an industrial site with power plants and a port in the city of Brindisi (Apulia Region, Southern Italy) reported a higher prevalence rate of total CAs, in particular of CHDs, than those reported by the 2011 pool of EUROCAT registries.[31,32] Specifically, the study observed an increased risk for VSDs and PVS, but not for atrial septal defects (ASDs). The overall risk for CHDs was higher in the city of Brindisi compared to the surrounding municipalities within the same province.[31] A further case-control study in Brindisi reported a risk association between the maternal residence exposure to SO_2 during weeks 3-8 of pregnancy and the occurrence of CHDs and VSDs, with an excess in the 2nd tertile and no trend from the 1st to the 3rd tertile. In the same study, no correlation between mother's exposure to fine particle and CHDs or VSDs emerged.[33]

A descriptive study on the municipality of Gela (Sicily Region, Southern Italy) – an industrial site with chemical plants, a thermoelectric plant, and a large refining plant – carried out between 2003 and 2008 detected an excess compared to the mean value obtained from Italian and European registries for genital organs malformations and for urinary tract defects, including non-specified diagnoses. The study showed an increase of cases with hypospadias compared to the European and Italian reference values, as well as an increase in limb malformations (including non-specified clubfoot), which was higher when compared with data from other areas of Italy. On the contrary, a decrease of lip and cleft palate in comparison to the European data was reported, even if it is difficult to explain and could be indicative of a failure to report or of a loss of documentation (table 2).[34]

LOCATION	STUDY DESIGN	STUDY SAMPLE (PERIOD)	MAIN RESULTS (95%CI)	ASSESSED OUTCOME	EXPOSURE ASSESSMENT	CONFOUNDING VARIABLES	REFERENCE
INDUSTRIES							
Colorado (USA)	Cohort LB	124,842 live births (1996-2009)	aOR: 1.2 (1.0-1.3) aOR: 1.3 (1.2-1.5) aOR: 1.5 (1.1-2.1) aOR: 1.5 (1.1-2.1) aOR: 1.6 (1.1-2.2) aOR: 3.9 (1.3-11) aOR: 4.2 (1.3-13) aOR: 2.0 (1.0-3.9)	CHD CHD VSD PVS PVS Tricuspid valve defects Tricuspid valve defects NTD	Average High High Average High Average High High	Newborn gender, maternal age, active smoking, educational level, smoking, alcohol consumption, number of births	McKenzie 2014[29]
Texas (USA)	Case-control LB; FD; ET	60,613 cases 244,927 controls (1996-2008)	aOR: 1.13 (1.04-1.22) aOR: 1.23 (1.10-1.37) aOR: 1.21 (1.07-1.38) aOR: 1.19 (1.06-1.32) aOR: 1.14 (1.02-1.28) aOR: 1.13 (1.05-1.21) aOR: 1.13 (1.02-1.24) aOR: 1.12 (1.01-1.24) aOR: 1.10 (1.01-1.19) aOR: 1.06 (1.02-1.10) aOR: 1.06 (1.04-1.09) aOR: 1.56 (1.11-2.18) aOR: 1.49 (1.08-2.06) aOR: 1.42 (1.09-1.86) aOR: 1.40 (1.04-1.87) aOR: 1.39 (1.08-1.79) aOR: 1.29 (1.01-1.63) aOR: 1.28 (1.01-1.62) aOR: 1.94 (1.32-2.84) aOR: 1.78 (1.22-2.59) aOR: 1.78 (1.12-2.82) aOR: 1.70 (1.06-2.71) aOR: 1.64 (1.24-2.16)	CSD CSD CSD CSD CSD CSD CSD CSD CSD CSD CSD NTD NTD NTD NTD NTD NTD NTD Spina bifida Spina bifida Spina bifida Spina bifida Spina bifida	Carbon tetrachloride 1,1-etylene dichloride Propylene dichloride 1,2-dichloroethylene Tetrachlororethane Ethylchloride 1,2,3-trichloropropane 1,1,2-trichloroethane Chloroform Trichloroethylene Any type of solvent 1,1,2- trichloroethane 1,2,3-trichloropropane Carbon tetrachloride Cloroformium Ethylchloride Metilchloroform 1,2-etylene diclhoride 1,1,2- trichloroethane 1,2,3-trichloropropane Tetrachlororethane 1,1-ethylene dichloride 1,2-ethylene dichloride		Brender 2014[30]
Texas (USA)	Case-control LB; FD; ET	60,613 cases 244,927 controls (1996-2008)	aOR: 1.60 (1.01-2.53) aOR: 1.59 (1.18-2.14) aOR: 1.58 (1.15-2.19) aOR: 1.56 (1.18-2.07) aOR: 1.55 (1.10-2.20) aOR: 1.77 (1.05-2.9) aOR: 1.21 (1.01-1.45) **Mother's age >35 years** aOR: 1.27 (1.01-1.58) aOR: 1.13 (1.04-1.22) aOR: 1.43 (1.08-1.88) aOR: 1.13 (1.03-1.23) aOR: 2.46 (1.23-4.91) aOR: 2.49 (1.09-5.72) aOR: 1.66 (1.04-2.65) aOR: 1.93 (1.05-3.94) aOR: 1.50 (1.00-2.26) aOR: 1.81 (1.06-3.07) aOR: 2.50 (1.11-5.63) aOR: 1.66 (1.07-2.56) aOR: 1.53 (1.21-1.93) aOR: 1.38 (1.14-1.67) aOR: 1.92 (1.11-3.32) aOR: 1.22 (1.03-1.46) aOR: 1.37 (1.10-1.70)	Spina bifida Spina bifida Spina bifida Spina bifida Spina bifida Cleft palate Transversal limb reductions Obstructive heart defects CHD Obstructive heart defects CSD NTD Spina bifida Oro-facial clefts Cleft palate Oral clefts CL ± CP Spina bifida Oro-facial clefts CL ± CP Oro-facial clefts Oro-facial clefts Oro-facial clefts CL ± CP	1,2-dichloroethylene Ethylchloride Carbon tetrachloride Methylchloroform Chloroform Propylene dichloride Tetrachloroethylene Any type of solvent Trichloroethylene Trichloroethylene Trichloroethylene Carbon tetrachloride Carbon tetrachloride Carbon tetrachloride 1,2-etylene diclhoride 1,2-etylene diclhoride Ethylchloride Ethylchloride Ethylchloride Methylchloride Methylchloride 1,2,3-trichloropropane Any type of solvent Any type of solvent		Brender 2014[30]
Brindisi (Italy)	Ecological LB	8,503 live births 194 cases (2001-2010)	RR: 1.42 (1.07-1.89) RR: 2.68 (1.33-5.33) RR: 1.80 (1.34-2.41) RR: 1.49 (1.20-1.85) ***vs.* outlying municipalities** aOR: 1.85 (1.36-2.50)	CAs PVS VSD CHD CHD		Maternal age, deprivation index	Gianicolo 2012[31]
Brindisi (Italy)	Case-control LB	189 cases, up to 4 controls per case (2001-2010)	cOR: 1.74 (1.07-2.81) cOR: 3.21 (1.42-7.25) cOR: 1.60 (0.70-3.62) cOR: 4.57 (1.31-15,96) cOR: 2.54 (0.62-7.40)	CAs CHD CHD VSD VSD	90th percentile SO_2 2nd tertile 3rd tertile 2nd tertile 3rd tertile		Gianicolo 2014[33]
Gela (Italy)	Ecological LB	5,993 live births 178 cases (2003-2008)	RR: 1.41 (1.21-1.63) *vs.* European value RR: 1.97 (1.69-2.27) *vs.* Italian value RR: 0.50 (0.23-0.95) *vs.* Italian value RR: 1.80 (1.19-2.53) *vs.* European value RR: 0.51 (0.23-0.97) *vs.* Italian value RR: 2.04 (1.43-2.76) *vs.* European value RR: 2.97 (2.08-4.02) *vs.* Italian value RR: 2.70 (1.86-3.70) *vs.* European value RR: 3.01 (2.07-4.13) *vs.* Italian value RR: 3.25 (1.05-7.58) *vs.* Italian value RR: 2.73 (1.81-3.84) *vs.* European value RR: 3.29 (2.18-4.62) *vs.* Italian value RR: 0.25 (0.03-0.90) *vs.* European value RR: 1.61 (1.20-2.08) *vs.* Italian value	CAs CAs Limbs (except for club foot n.s.) Limbs (including club foot n.s.) Urinary (except for pielectasia n.s.) Urinary (including pielectasia n.s.) Urinary (including pielectasia n.s.) Genitals (total) Genitals (total) Genitals (except hypospadias) Hypospadias Hypospadias CL CHD			Bianchi 2014[34]

aOR: adjusted odds ratio / *odds ratio aggiustato;* **CAs:** congenital anomalies / *anomalie congenite;* **CHD:** congenital heart defects / *difetti cardiaci congeniti*; **CI:** confidence interval / *intervallo di confidenza*; **CL:** cleft lip / *labioschisi*; **CP:** cleft palate / *palatoschisi*; **CSD:** cardiac septal defects / *difetti cardiaci del setto*; **ET:** elective termination / *interruzione volontaria di gravidanza*; **FD:** foetal death / *morte fetale*; **LB:** live birth / *nato vivo*; **n.s.:** not specified / *non specificato*; **NTD**: neural tube defects / *difetti del tubo neurale*; **PVS:** pulmonary valve stenosis / *stenosi valvolare polmonare*; **RR:** relative risk / *rischio relativo*; **VSD:** ventricular septal defects / *difetti del setto ventricolare*

Table 2. Proximity to industrial areas and risk of congenital anomalies.
Tabella 2. Prossimità residenziale a siti industriali e rischio di anomalie congenite.

MINES
MINIERE

Coal mining activities are widespread across the Appalachian region of the United States (Kentucky, Tennessee, Virginia, and West Virginia) and they largely employ mountain-top mining (MTM) technique with ammonium-nitrate based explosives that causes the seepage of many metals such as arsenic (As), chromium (Cr), mercury (Hg), and lead (Pb) into the groundwater.[35] An ecological study performed within this area for the years 1996-2003 observed an increased prevalence rate ratio (PRR) of total anomalies and for six specific groups (central nervous system, circulatory/respiratory apparatus, gastrointestinal system, urogenital system, musculoskeletal system, "other CAs") in the counties with marked MTM activities. Other mining sites showed an increasing in PRR values compared with unexposed areas exclusively for urogenital anomalies and "other CAs" (table 3).[36] A hospital-based case-control study carried out in West Virginia suggested a higher PRR value in the MTM counties compared with the non-mining areas, when data were not adjusted for the delivery hospital, suggesting that the increase in CAs prevalence was a consequence of the bias introduced by the birth centre.[37]
A small cross sectional study performed in Bolivia in 2006 aimed to evaluate whether the local Weenhayek population, living in proximity to lead and cadmium mine, had an increased risk for reproductive adverse outcomes including CAs (especially, hemangiomas and lymphangiomas) and development disorders compared with the control population. The study did not observe increased risk of CAs.[38]

LOCATION	STUDY DESIGN	STUDY SAMPLE (PERIOD)	MAIN RESULTS (95%CI)	ASSESSED OUTCOME	CONFOUNDING VARIABLES	REFERENCE
MINES						
Kentucky, Tennessee, Virginia, West Virginia (USA)	Ecological LB	1,889,071 live births 28,701 cases (1996-2003)	**MTM areas *vs.* control areas** aPRR: 1.26 (1.21-1.32) **non MTM areas *vs.* control areas** aPRR: 1.10 (1.05-1.16) **MTM areas *vs.* control areas** aPRR: 1.93 (1.73-2.15) aPRR: 1.36 (1.11-1.67) aPRR: 1.41 (1.17-1.71) aPRR: 1.35 (1.19-1.54) aPRR: 1.30 (1.20-1.41) aPRR: 1.13 (1.04-1.23) **non MTM areas *vs.* control areas:** aPRR: 1.32 (1.15-1.51) aPRR: 1.12 (1.03-1.22)	CAs CAs Cardio respiratory system Central nervous system Gastrointestinal system Urogenital system Musculoskeletal system Other CAs Urogenital system Other CAs	Maternal age, active smoking, newborn gender, years of schooling, folic acid intake, alcohol consumption, smoking, gestational diabetes, maternal residence in a metropolitan area	Ahern 2011[36]
West Virginia (USA)	Ecological LB	418,385 live births (1990-2009)	**Analysis on 44 hospitals:** cPRR: 1.43 (1.35-1.51); p<0.001 aPRR: 1.08 (0.97-1.20); p=0.16 **Analysis on 6 hospitals with more than 1,000 births:** cPRR: 2.39 (2.15-2.65); p<0.001 aPRR: 1.01 (0.69-1.17); p=0.87	CAs	Hospital birthplace	Lamm 2015[37]
Pilcomayo river (Bolivia); Bermejo river (Argentina)	Cross-sectional LB; FD	191 cases 107 controls (2006)	aOR: 2.60 (0.7-9.2)	CAs	Maternal age	Stassen 2012[38]

aOR: adjusted odds ratio / *odds ratio aggiustato*; **aPRR:** adjusted prevalence rate ratio / *tasso di prevalenza aggiustato*; **CAs:** congenital anomalies / *anomalie congenite*; **CI:** confidence interval / *intervallo di confidenza*; **cPRR:** crude prevalence rate ratio / *tasso di prevalenza crudo*; **FD:** foetal death / *morte fetale*; **LB:** live birth / *nato vivo*

Table 3. Proximity to mines areas and risk of congenital anomalies.
Tabella 3. Prossimità residenziale a miniere e rischio di anomalie congenite.

LANDFILLS
DISCARICHE

A review of epidemiological studies[39] – which followed the International Agency for Research on Cancer (IARC) criteria in the attempt to evaluate the evidence of cause-effect relation between landfills exposure and the risk of CAs[40] – concluded that the reviewed literature provided limited evidence. Overall, this review collected 18 papers published in the years 1992-2010 (table 4). The review covered 10 ecological studies, 1 cohort study, and 7 case-control studies (2 of which were multicentre studies). Three single-site ecological studies were conducted in England. Whilst an increase in prevalence of CAs in babies born to mothers residing in proximity of a landfill was reported in the first of these 3 studies, the risk increased similarly both before and after the opening of the landfill site, suggesting possible involvement of other sources of exposure.[41] In the second study, an increase in CAs prevalence among newborns in proximity of a landfill treating hazardous, domestic, and commercial wastes emerged.[42] The third study did not find any association between CAs in newborns and distance of residence from chromium-contaminated site.[43] In two multisite ecological studies conducted in England, a weak increase in NTDs, hypospadias and epispadias, abdominal wall defects, surgical correction of gastroschisis and exomphalos, and a weak prevalence decrease of CHDs were reported among babies born to mothers living less than 2 km from special and non-special waste landfills. For specific anomalies, especially for hospital admissions for abdominal wall defects, risks were higher in the period before the opening of a landfill site compared with the period after the opening.[44,45] A multisite ecological study carried out in the UK did not observe any associations between CA risk and residential proximity to 61 sites of hazardous waste landfills.[46]

Another multiple-site ecological study carried out in Washington State showed an increased overall risk of CA and skin anomalies in offspring of communities living less than 8 km from landfills processing hazardous waste.[47] Palmer's study found that the number of observed CA cases, compared with the expected, increased by 40% after the opening of landfill sites located within 4 km from residence.[48] A multisite ecological study conducted in Denmark on people residing less than 2 km from one of the 48 landfill sites showed a slight increase in the risk of CHDs, compared with the populations living 2-4 km or 4-6 km away from the landfill sites.[49] This result was not confirmed after the normalization of aggregated data, except for an increased risk of nervous system defects.[49] A Brazilian ecological study performed on the areas surrounding the 15 landfills in San Paolo did not observe any increase in the risk of total CAs among children up to one year of age born to mothers residing within 2 km from a landfill.[50] The lack of an association was reported in a cohort study conducted in an area with 196 landfill sites in Cumbria (England).[51] The multicentre case-control study EUROHAZCON – which aimed to study the risk of congenital anomalies near hazardous-waste landfill sites in Europe – detected a moderate increase for transposition of great arteries (TGA), CSDs, and NTDs among babies born to mothers living within 3 km from landfill sites containing hazardous chemical waste compared with those of mothers living within a 3-7 km radius from the same sites.[52] In a further multicentre study, no association was found even if at each study area was attributed a specific risk coefficient based on the site characteristics.[53] A case-control study carried out in California on 48 sites stocking hazardous waste did report no CAs increases among offspring.[54] Similarly, an Irish case-control study did not observe associations between proximity to landfill of urban waste and CAs prevalence.[55]

An American case-control multisite study showed an increase in the risk of anomalies of CNS, musculoskeletal disorders, and skin malformations among newborns to mothers residing within a 1.6 km radius from one of the 590 landfills containing toxic wastes. The study reported a dose-response relationship.[56] In contrast, a United States case-control study reported a weak association for CNS defects and musculoskeletal system disorders in offspring of mothers living nearby sites producing dangerous emissions (solvents, metals, pesticides).[57] A previous case-control study conducted in the United States did not show any increase in risk of NTDs as a group or of oro-facial clefts in babies born to mothers living within 0,4 km from at least one of the 764 hazardous waste sites.[58]

The review by Triassi et al. relating to the effects of waste disposal on human health found only 2 studies published in 2008-2009 concerning the risk of CAs associated with both legal and illegal disposal of waste. These studies investigated areas in the provinces of Naples and Caserta (Campania Region, Southern Italy), characterized by illegal waste disposal and by the presence of other environmental contaminant sources (intensive agriculture, industrial activities, high population density), and concluded that further studies were needed to detect any possible causal relation.[59] The first study reported the presence of clusters with an excess of prevalence of total CAs (five clusters), urogenital malformations (three cluster), CHDs (two clusters), and limb malformations (one cluster).[60] A second ecological study carried out in the same provinces reported a negative trend between the risk of CHDs and exposure, while observed a positive association with the socioeconomic deprivation index. An excess of urogenital cases and CNS defects for the highest percentile levels of exposure was also detected.[61]

LANDFILLS

LOCATION (NUMBER)	STUDY DESIGN	STUDY SAMPLE (PERIOD)	MAIN RESULTS (95%CI)	ASSESSED OUTCOME	EXPOSURE ASSESSMENT	CONFOUNDING VARIABLES	REFERENCE
LANDFILLS							
UK (No. 8) Europe (No. 2) USA (No. 5) Ireland (No. 1) Brazil (No. 1) Denmark (No. 1)	**Systematic review:** • ecological (No. 10) • case-control (No. 2) **Multicentre:** • case-control (No. 5) • cohort (No. 1)	18 studies (1992-2010)	**Single site study:** RR: 1.9 (1.30-2.85) RR: 1.9 (1.23-2.95) RR: 1.9 (1.30-2.90) **Multisite studies:** RR 1.39 (1.12-1.72) aOR: 1.33 (1.11-1.59) RR: 1.07 (1.04-1.09)* RR: 1.02 (1.01-1.03)* aOR: 1.33 (1.27-1.40) aOR: 1.28 (1.22-1.35) aOR: 1.26 (1.20-1.32) aOR: 1.15 (1.10-1.21) aOR: 1.08 (1.02-1.13) aOR: 2.46 (2.27-2.68) aOR: 2.39 (2.16-2.65) aOR: 1.86 (1.24-2.79) RR: 1.05 (1.01-1.10)* RR: 1.06 (1.01-1.12)* aOR: 1.49 (1.09-2.04) aOR: 1.81 (1.02-3.20) RR: 0.96 (0.93-0.99)* aOR: 1.16 (1.00-1.33) RR: 1.18 (1.03-1.34)* RR: 1.08 (1.01-1.15)* RR: 1.07 (1.04-1.10)* aOR: 1.12 (1.02-1.22)	 CAs CAs CAs CAs CAs CAs CAs CAs CAs CAs Skin anomalies Skin anomalies NTD NTD NTD CSD TGA CHD CHD Gastroschisis and omphafalocele Abdominal wall defects Hypospadias and epispadias Hypospadias and epispadias	 Urban and industrial waste (before/after the opening of the plants) Urban and industrial waste (after the opening of the plants) Urban, commercial, and industrial waste Urban and Industrial waste (before/after the opening of the plants) Hazardous waste < 3 km Special waste and non-special waste Hazardous waste d < 0,8 km Hazardous waste 0.8 < d < 1.6 km Hazardous waste 0.6 < d < 3.2 km Hazardous waste 3.2 < d < 8.0 km Special waste (3rd quartile *vs.* 1st quartile) Low risk sites All sites Hazardous waste < 3 km Special and non-special waste Special and non-special waste Hazardous waste < 3 km Hazardous waste < 3 km Special and non-special waste special waste (3° quartile) Special and non-special waste Special and non-special waste Special and non-special waste Special waste Special waste (4th quartile *vs.* 1st quartile)	Newborn gender, maternal age, smoking, weight at birth, length of pregnancy, complications during pregnancy, alcohol consumption, smoking, parity, folic acid intake, employment status, family income, town of residence	Mattiello 2013[39]
UK (No. 8) Europe (No. 2) USA (No. 4) Ireland (No. 1) Brazil (No. 1) Denmark (No. 1)	**Systematic review:** • ecological (No. 10) • case-control (No. 2) **Multicentre:** • case-control (No. 5) • cohort (No. 1)	18 studies (1992-2010)	aOR: 1.12 (1.06-1.18) aOR: 1.63 (1.34-1.99) aOR: 1.09 (1.04-1.15) aOR: 1.29 (1.05-1.59) aOR: 1.32 (1.18-1.48) aOR: 2.63 (1.31-2.49) aOR: 1.22 (1.08-1.38) aOR: 1.16 (1.06-1.26) aOR: 1.75 (1.31-2.34) aOR: 1.09 (1.00-1.18) aOR: 1.27 (1.03-1.57) aOR: 1.36 (1.08-1.72) **Risk ratio:** 1 (zone 0-2 km); 0.926 (zone 2-4 km); 0.854 (zone 4-6 km) p trend: 0.16	CAs CAs CAs CNS Skin anomalies Skin anomalies Skin anomalies Musculoskeletal system Musculoskeletal system Musculoskeletal system CNS CNS CHD	Hazardous waste Hazardous waste (high exposure) Hazardous waste (low exposure) Hazardous waste Hazardous waste Hazardous waste (high exposure) Hazardous waste (low exposure) Hazardous waste Hazardous waste (high exposure) Hazardous waste (low exposure) Hazardous waste + emissions industrial solvents Hazardous waste + emissions industrial metals Hazardous waste	Newborn gender, maternal age, smoking, weight at birth, length of pregnancy, complications during pregnancy, alcohol use, smoking, parity, folic acid intake, employment status, family income, town of residence	Mattiello 2013[39]
Campania (Southern Italy) (No. 2)	**Review:** • ecological (No. 2)	2 studies (2008-2009)	RR: 1.28-5.85 RR: 2.38-4.29 RR: 1.30 ERR: 82.7 (25.6-155.7) ERR: 83.5 (24.7-169.9) RR: 1.54-2.04 ERR: -5.3 (-9.4;-1.0) ERR: 12.5 (6.9-12.4)	CAs Urogenital system Limb reduction Urogenital system CNS CHD CHD CHD	Landfills + illegal waste landfills	Deprivation index, exposure Index	Triassi 2015[59]

***** 99% confidence interval / *intervallo di confidenza al 99%*

aOR: adjusted odds ratio / *odds ratio aggiustato*; **CAs:** congenital anomalies / *anomalie congenite*; **CHD:** congenital heart defects / *difetti cardiaci congeniti*; **CI:** confidence interval / *intervallo di confidenza*; **CNS:** central nervous system / *sistema nervoso centrale*; **CSD:** cardiac septal defects / *difetti cardiaci del setto*; **ERR:** excess relative risk / *eccesso di rischio relativo*; **NTD:** neural tube defects / *difetti del tubo neurale*; **RR:** relative risk / *rischio relativo*; **SES:** socioeconomic status / *livello socioeconomico*; **TGA:** transposition of great arteries / *trasposizione dei grossi vasi*

Table 4. Proximity to landfills and risk of congenital anomalies.
Tabella 4. Prossimità residenziale a discariche e rischio di anomalie congenite.

INCINERATORS
INCENERITORI

The association between maternal residential proximity to incinerators and CA risk was evaluated in a review of 7 published studies conducted between 1998 and 2010. The review found associations only for selected CA subgroups and concluded that literature provided limited evidence and that further studies were necessary (table 5).[62] In particular, a French ecological study observed an excess of risk for cleft lip/palate and kidney dysplasia among the population living in proximity to solid waste incinerators. An increase of relative risk of conotruncal heart malformations and other CHDs was observed.[63] Another French study reported an increased risk for urinary tract defects in the offspring of exposed mothers. This study investigated maternal exposure to airborne dioxins and dioxin deposits starting a month before conception until the last trimester of pregnancy.[64] In a Swedish ecological study, no association between maternal exposure to dioxins and the risk of cleft lip and palate among offspring were observed.[65]

An ecological study carried out in England in a population residing close to a waste combustion plant did not report any increase in CAs as a group.[66] In contrast, a cohort study found a slight increase in risk for CHDs and NTDs (particularly spina bifida and anencephaly) among offspring of mothers living in proximity to incinerators or cremating incinerators.[67] Lastly, two studies carried out in Italy (a cohort study and a case-control study) showed no increased risk of CAs, both as CAs overall and as specific anomaly subgroups, among newborns born to mothers exposed to municipal urban solid waste incinerator emissions.[68,69]

LOCATION (NUMBER)	STUDY DESIGN	STUDY SAMPLE (PERIOD)	MAIN RESULTS (95%CI)	ASSESSED OUTCOME	EXPOSURE ASSESSMENT	CONFOUNDING VARIABLES	REFERENCE
INCINERATORS							
France (No. 2) UK (No. 2) Italy (No. 2) Sweden (No. 1)	**Systematic review:** • cohort (No. 2) • case-control (No. 2) • ecological (No. 3)	7 studies (1998-2010)	RR: 1.30 (1.06-1.59) RR: 1.55 (1.10-2.20) aOR: 1.83 (1.13-2.96) aOR: 2.95 (1.47-5.92) aOR: 1.99 (1.17-3.40) aOR: 2.84 (1.32-6.09) aOR: 1.13 (1.04-1.23) aOR: 1.17 (1.07-1.28) aOR: 1.23 (1.01-1.50) aOR: 1.12 (1.03-1.22) aOR: 1.12 (0.90-1.40) aOR: 1.02 (0.87-1.20)	Oro-facial cleft Renal dysplasia Urinary anomalies Urinary anomalies Urinary anomalies Urinary anomalies NTD Spina bifida Anencephaly CHD Conotruncal CHD	Solid urban waste Solid urban waste Dioxin deposits Dioxin deposits – above the median Airborne dioxins Airborne dioxins – above the median After the opening of the incinerator After the opening of the incinerator ≤3 km from the cremating ovens After the opening of the incinerator Solid urban waste Solid urban waste	Newborn's year of birth, newborn gender, town of birth, maternal age, maternal ethnicity, educational level, parity, maternal job, folic acid intake, treatment of chronic disease during first trimester, obesity, smoking, antiepileptic drugs, tobacco use, consanguinity, alcohol consumption, population density, deprivation index, multiple births, average family income, other sources of dioxin, car traffic, previous exposure to incinerator emissions	Ashworth 2014[62]

aOR: adjusted odds ratio / *odds ratio aggiustato*; **CHD:** congenital heart defects / *difetti cardiaci congeniti*; **CI:** confidence interval / *intervallo di confidenza*; **NTD:** neural tube defects / *difetti del tubo neurale*; **RR:** relative risk / *rischio relativo*

Table 5. Proximity to incinerators and risk of congenital anomalies.
Tabella 5. Prossimità residenziale a inceneritori e rischio di anomalie congenite.